Overview of Metabolic Disorders
(aka Inborn Errors of Metabolism)

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What are Inborn Errors of Metabolism?
- Genetic disorders that affect the breakdown of food
  - Food that is not broken down properly may produce chemicals that build up in various parts of the body, causing medical problems and learning disorders, including cognitive impairments which can sometimes be very severe if untreated
  - Missing or non-working enzymes (proteins) necessary to break down the food eaten
- They are genetic (inherited) disorders
  - Each parent is a “carrier” of a non-working trait that is passed down to their child
- Prompt and proper treatment can prevent/lessen symptoms

Effects of an Enzyme Defect

Types of Inborn Errors
- Protein Disorders
  - Amino acids (Phenylketonuria, Maple Syrup Urine Disease)
  - Organic acids (Methylmalonic Aciduria, Biotinidase Deficiency)
  - Urea cycle (Citrullinemia, Argininosuccinic Aciduria)
- Carbohydrate Disorders
  - Galactosemia
- Fatty Acid Disorders
  - Medium Chain Acyl CoA Dehydrogenase Deficiency (MCAD)
  - Very Long Chain Acyl CoA Dehydrogenase Deficiency (VLCAD)

Goals of Medical Nutrition Strategy
- Two fold approach
  - Acute/emergency management
  - Long term management
- Maintain biochemical balance
- Careful monitoring to ensure adequate nutrition (protein and calories) for growth and development
Medical Management/ Follow-up

- All positive screens for inborn error of metabolism referred to (CHMMC)
  - Notification to local MDs
  - CHMMC staff contacts primary medical doctor with recommendations for treatment/intervention
  - Metabolic physician on call 24 hours/7 days/week to assist in either long distance management or transfer to CHM

Current Treatment Strategies for Metabolic Disorders

Accumulation of toxic substance?
**Restrict amount available**

Absence of important product?
**Supplement product or cofactor**

Both?
**Combine all approaches**

Amino Acid Disorders - Treatment - “Diet for Life”

- Early diagnosis (newborn screening) critical for successful treatment
- Phenylketonuria: mutations in gene coding for **phenylalanine hydroxylase** → deficient enzyme activity
  - Excess phenylalanine
    - (accumulation of substrate)
    - Phenylalanine → phenylpyruvic acid
    - (accumulation of alternate product)
  - Deficiency of tyrosine → deficiency of neurotransmitters dopamine and norepinephrine
    - (deficiency of product)

Amino Acid Disorders - Treatment - “Diet for Life”

- Prevent phenylalanine accumulation via phenylalanine-restricted diet
  - Provide enough phenylalanine for normal growth using phe-free metabolic formula + dietary restrictions/low protein products

Urea Cycle Disorders: Diagnosis and Treatment (“Diet for Life”)

- **↓ amount of NH₃ made**
  - Protein restriction

- **↑ amount of NH₃ removed**
  - Alternative pathways (divert NH₃ from urea production, thereby ↓ plasma NH₃)
  - Supplemental arginine or citrulline to treat deficiency (i.e. “prime the pump”)
**Organic Acid Disorders**

- Most are disorders of amino acid metabolism
- Some caused by mutations in cofactors (biotinidase)
- Most are enzyme defects (isovaleric acidemia, propionic acidemia, methylmalonic acidemia)
- Treatment (“Diet for Life”)
  - restrict substrate (protein/amino acids)
  - avoid protein breakdown
  - provide required cofactors

**Coenzyme Defects**

- Disorders due to defects in cofactor (vitamin)
  - Many enzymatic reactions depend on coenzymes that function as cofactors
  - Defect in cofactor can lead to metabolic block
- Diagnosis of specific inborn error is essential
  - Some inborn errors are “curable” by treating patient with large doses of cofactor, such as biotin for patients with biotinidase deficiency

**Disorders of Carbohydrate Metabolism (Galactosemia)**

- Characterized by defects in carbohydrate (sugar) metabolism such as glucose, fructose and galactose
  - Galactose is a component of lactose, the primary sugar component in human breast milk and cow’s milk
- Treatment: minimize galactose accumulation
  - Remove lactose from diet (primarily milk products)
  - Use soy-based formulas, milk substitutes

**Fatty Acid Oxidation Disorders**

- Fats are required to help produce glucose (energy) needed by all cells
  - A block in pathway leads to low blood sugar levels (hypoglycemia)
- Medium Chain Acyl CoA Dehydrogenase Deficiency (MCAD)
  - Treatment
    - Heart-healthy diet (lower in offending fats)
    - Avoidance of fasting to prevent hypoglycemia

**Treatment for Metabolic Disorders: Toxic Accumulation**

- Diet management
  - PKU – restrict protein, specifically phenylalanine
  - Galactosemia – restrict galactose
  - VLCAD – restrict “long chain” fatty acids
- Drugs that bind or eliminate toxic product
  - Buphenyl for urea cycle disorders
- Specific vitamins (cofactors) that help enzyme do its job
  - biotin for biotinidase deficiency

**Medical Progress**

*“Doctor, I have an earache”*

- 2000 BC  “Here, eat this root.”
- 1000 BC  “That root is heathen; say this prayer.”
- 1850 AD  “Prayer is superstition; drink this potion.”
- 1940 AD  “That potion is snake oil; swallow this pill.”
- 1990 AD  “That pill has a narrow therapeutic window and low efficacy; take this biologically engineered drug.”
- 2000 AD  “That drug is artificial. Here, eat this root.”